35 U.S.C § 103(a): Claims 1-31

The Examiner rejected Claims 1-31 under 35 U.S.C. § 103(a) as being unpatentable over Hamanaka. In particular, the Examiner contends that Hamanaka generically discloses a pyrazole-carbonyl guanidine compound for treating ischemia (Claims 1 and 102). The Examiner contends that a specific compound, [5-cyclopropyl-1-quinolin-5-yl)-1H-pyrazole-4-carbonyl]-guanidine, is described in Claim 103. The Examiner further argues that the instant compound differs from Hamanaka's compound in having an additional 2-hydroxy (which tautomerizes to 2-oxo) on the quinolinyl moiety. The Examiner further states that Hamanaka also teaches that 2-hydroxy is an optional substituent among a small genus in Claim 102. Accordingly, the Examiner reasons that one of ordinary skill in the art would be motivated to add the optional 2-hydroxy onto the quinolinyl of the [5-cyclopropyl-1-quinolin-5-yl)-1H-pyrazole-4-carbonyl]-guanidine to arrive at the instant invention. The Examiner contends that in the absence of unexpected results, the instant invention is prima facie obvious.

Applicants traverse the 35 U.S.C. § 103(a) rejection of Claims 1-31 and respectfully request that the Examiner withdraw her rejection and allow the claims. Notwithstanding, the objection, Applicants have attached hereto a 1.132 Declaration of Mary C. Allen in which data is submitted, demonstrating the unexpected results of the instant invention. In particular, Ms. Allen states that the claimed Formula I compound (described therein as "Compound B" in Ms. Allen's Declaration), has an almost two-fold half-life over the compound disclosed in Hamanaka, which is an unexpected superior property in that greater flexible dosing regimens are possible. Furthermore, the longer-lasting half-life of the claimed compound provides for a longer duration of action that is superior to the compound disclosed by Hamanaka.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the 35 U.S.C. § 103(a) rejection of Claims 1-31.

35 U.S.C § 103(a): Claims 1-29 and 31

The Examiner rejected Claims 1-29 and 31 under 35 U.S.C. § 103(a) as being unpatentable over Hamanaka (WO 99/43663) in view of Munson and Beedham. In particular, the Examiner states that Hamanaka discloses [5-cyclopropyl-1-quinolin-5-yl)-1H-pyrazole-4-carbonyl]-guanidine in Claim 103. As alleged in the prior rejection, the Examiner contends that the instant compound differs from Hamanaka's compound in having an additional 2-hydroxy (which tautomerizes to 2-oxo) on the quinolinyl moiety. According to the Examiner, the instant compound is the oxidation metabolite of the Hamanaka compound. The Examiner further states that the hydroxylation reaction is well known in the pharmaceutical art as one of the phase I metabolic transformations of drugs (Munson) and

specifically described by Beedham. Consequently, the Examiner states that the instant compound is prima facie obvious, in the absence of unexpected results.

Applicants traverse the 35 U.S.C. §103(a) rejection of Claims 1-29 and 31 and respectfully request that the Examiner withdraw her rejection and allow the claims. In particular, while hydroxylation is known in the art as one of the phase I metabolic transformations of drugs, the ultimate metabolic disposition is unpredictable. In fact, as noted, as noted by Munson, "[t]he chemical modification of drugs during the course of metabolism may result in complete or partial loss of pharmacologic activity." (Munson at p. 53.)

As described in Munson, there are many different enzymes involved in the metabolism of drugs and other xenobiotics that may catalyze a variety of reactions, at many potential substrates. In particular, it is known that different enzymes can work in concert, but have varying degrees of substrate selectivity (which substrates they work on), chemoselectivity (which functional group they metabolize) and positional selectivity (what position of the molecule is metabolized). Accordingly, the large diversity of enzymes and potential metabolic reactions make it very difficult for one of ordinary skill in the art to predict the extent and type of metabolism that a specific compound will undergo – if it occurs at all.

Moreover, even if metabolism occurs, the compound may still undergo phase I or phase II metabolism, of which multiple types of phase I transformations may occur. (See Table 2.5 for a list of typical Phase I metabolic transformations – none of which specify oxidation at the 2-position of a quinolone moiety). For example, even if hydroxylation is identified as occurring in a specific compound, the hydroxylation may take place at a variety of atoms, such as, *inter alia*, nitrogen, sulfur, saturated carbon or aromatic carbon. Additionally, hydroxylation may occur at different positions in an aromatic ring. Furthermore, a single compound can be the substrate for multiple competing transformation reactions. Consequently, one of ordinary skill in the art could not predict (1) the likelihood of metabolism, (2) the type of metabolism, (3) the extent of metabolism, and (4) the position of metabolism in a molecule, without extensive experimentation.

Accordingly, in the instant invention, in the case of the cited prior art Hamanaka compound (described as Compound A in the attached Declaration), a person of ordinary skill in the art could not predict (1) whether metabolism would occur, (2) where the metabolism would occur, (3) what type of metabolism would occur, and (4) what the pharmacological effect would be. For example, based upon Munson's disclosure, the Hamanaka compound could potentially be conjugated, hydrolyzed or oxidized at the acylguanidine portion. Alternatively, oxidation could occur at one or more of the nitrogen atoms of the Hamanaka compound. Furthermore, hydroxylation could occur at any of the carbons of the cyclopropyl

ring or any of the seven aromatic carbons. Finally, as discussed in Munson, metabolism of the Hamanaka compound may be a combination of any of the above reactions.

Accordingly, one of ordinary skill in the art would not be motivated by Munson to expect that a biotransformation may occur at the 2-position of the quinoline ring of the instant invention. Instead, Munson teaches the unpredictability of transformations. A transformation may or may not occur. Complete or partial loss of pharmacological activity may or may not occur. Furthermore, if in fact a biotransformation was predictable, one of ordinary skill in the art still could not predict where and what type of biological transformation may occur, since, *inter alia,* hydroxylation, epoxidation, and demethylation are all possible metabolic disposition routes.

While Beedham does disclose oxidation at the 2-position of a quinoline ring, the compounds disclosed therein are dissimilar to the Applicants' claimed compounds. In particular, the instant compounds comprise moieties not shared by the compounds disclosed in Beedham. As disclosed by Munson, a wide variety of mechanisms may occur during metabolism, as well as a wide variety of different substrates may be vulnerable to transformation. As such, while the instant invention and Beedham share a quinolone moiety, different groups on the respective compounds may also be metabolized instead or in addition to the group in question to provide very different compounds. Accordingly, one skilled in the art could not predict whether the metabolic path observed by Beedham for substantially different compounds would be similar to the metabolic path observed for the Hamanaka compound.

Consequently, a person skilled in the art would not be motivated to combine the disclosures of Hamanaka, Munson and Beedham to arrive at the instant invention. As noted by the Federal Circuit, the requisite motivation must come from the prior art, not Applicants' specification. In re Dow Chem. Co., 837 F.2d 469, 473, 5 USPQ.2d 1529, 1531-1532 (Fed. Cir. 1988). Additionally, the references do not expressly or impliedly suggest the combination described in Applicants' invention. Furthermore, Munson, certainly, provides no reasonable expectation of success that a combination of the references may result in the instant invention.

Claims 1-29 and 31 are, therefore, not obvious over Hamanaka in view of Munson and Beedham. Notwithstanding the above, as stated in the preceding response, a declaration of Ms. Allen is attached, setting forth the superior properties of the instant compound over the Hamanaka compound. These properties are unexpected and were unpredictable. Consequently, Applicants are entitled to the selection invention as described in the claims at issue.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the 35 U.S.C. § 103(a) rejection of Claims 1-29 and 31.

Provisional Obvious-Type Double Patenting:

Hamanaka Reference. The Examiner provisionally rejected Claims 1-31 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the corresponding claims of co-pending Application No. 09/367731 (Hamanaka; WO 99/43663). The Examiner states that atlthough the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are encompassed by the copending claims and for the reasons set forth in the 35 U.S.C. § 103(a) rejections.

The Examiner also provisionally rejected Claims 1-29 and 31 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the corresponding claims of Hamanaka in view of Munson and Beedham. The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth in paragraph 5 of the 35 U.S.C. § 103(a) rejection.

Applicants traverse both of the provisional obviousness-type double patenting rejections of Claims 1-31 and Claims 1-29 and 31 and respectfully request that the Examiner withdraw her rejection and allow the claims.

A double-patenting rejection cannot be justified solely on the ground that the subject matter of the claims in the instant application are dominated by the claims in a first patent, Hamanaka. The Federal Circuit has reversed double-patenting rejections and held as follows:

> By domination we refer, in accordance with established patent law terminology, to that phenomenon, which grows out of the fact that patents have claims, whereunder one patent has a broad or "generic" claim which "reads on" an invention defined by a narrower or more specific claim in another patent, the former "dominating" the latter because the more narrowly claimed invention cannot be practiced without infringing the broader claim. . . . This commonplace situation is not, per se, double patenting as the [Examiner] seemed to think.

In re Kaplan, 789 F.2d 1574, 229 USPQ 678, 681 (Fed. Cir. 1986). Consequently, the presence of dominating claims in Hamanaka is not the determining factor in nonstatutory-type double patenting rejections.

Generally, a "one-way" test is applied to determine obviousness-type double patenting. In doing so, the question is whether the application claims are obvious over the prior art claims. In re Goodman, 11 F.3d 1046, 29 USPQ.2d 2010, 2015-16 (Fed. Cir. 1993). For the reasons articulated above in Applicants' response to the 35 U.S.C. § 103(a) rejections, Applicants reiterate that Claims 1-31 are unobvious in light of the unexpected

favorable half-life properties demonstrated by the instant invention compared to the prior compound. At the time of the filing of the Hamanaka application, the instant claimed invention and its properties were not known. It was only subsequent to the filing of the Hamanaka application that Applicants arrived at the instant invention and demonstrated the superior properties of the instant invention compared to the Hamanaka prior art compound.

Accordingly, Applicants are entitled to a selection patent. Applicants respectfully request, therefore, that the Examiner reconsider and withdraw the provisional obviousness-type double patenting rejections of Claims 1-31.

Co-pending Application 09/657,254. The Examiner provisionally rejected Claims 1-31 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the corresponding claims of co-pending Application No. 09/657,254. The Examiner states that even though the conflicting claims are not identical, they are not patentably distinct from one another. According to the Examiner, the co-pending crystalline form of the instant quinolone compound is prima facie obvious over the instant compound, and that in the absence of unexpected results, merely changing the physical form of the compound does not render the compound unobvious, especially when the utility remains the same.

Applicants traverse the provisional obviousness-type double patenting rejection of Claims 1-31 and respectfully request that the Examiner withdraw her rejection and allow the claims.

In particular, Applicants respectfully point out that co-pending Application No. 09/657,254 is not the crystalline form of the instant quinolone compound. The compound claimed in 09/657,254 is the mesylate salt of the cited prior art Hamanaka compound, N-(5-cyclopropyl-1-quinolin-5-yl-1H-pyrazole-4-carbonyl)-guanidine, monomesylate salt. Accordingly, the compounds claimed in Application No. 09/657254 are not mere changes in the physical form of the instant invention.

As discussed above, Applicants demonstrated the superior properties of the 2-carbonyl on the quinolinyl moiety compared to the unsubstituted. Accordingly, the instant invention is not obvious over the co-pending 09/657,254 application.

Applicants respectfully request, therefore, that the Examiner reconsider and withdraw the provisional obviousness-type double patenting rejections of Claims 1- 31.

CONCLUSION

The points and concerns raised by the Examiner having been fully addressed, Applicants urge that this application is in condition for allowance, which action is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment.

Respectfully Submitted,

Date: 11-16-01

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Please cancel claim 30.